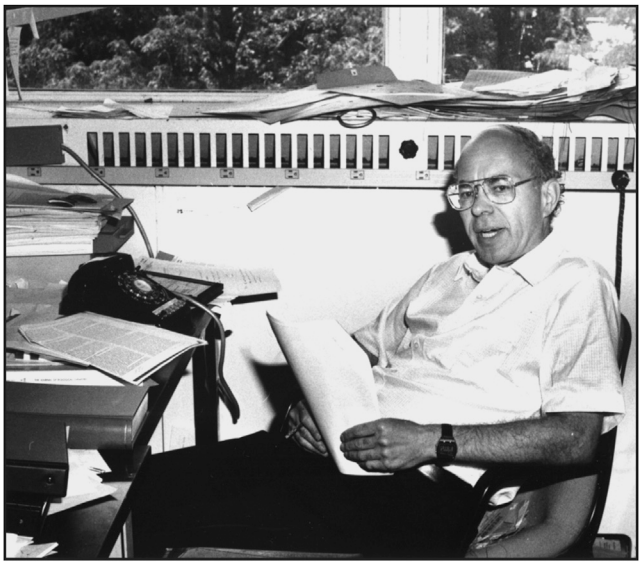
Cell

Irwin (Ernie) Allen Rose (1926-2015)

In 1953, while still at Tufts College Medical School, Mel Simpson published a landmark paper demonstrating the ATP dependence of intracellular protein degradation. A year later, after moving to the Department of Biochemistry at Yale University Medical School, Simpson described his enigmatic results in a late-night discussion with a newly minted Instructor recently arrived from post-doctoral training. Fifty years later, that young faculty member, Ernie Rose, would share the 2004 Nobel Prize in Chemistry with Avram Hershko and Aaron Ciechanover for explaining Simpson's mystery. Their seminal discovery of ubiquitin-dependent protein degradation has proved as significant in our understanding of cellular regulation as the earlier discovery of protein phosphorylation. Sadly, Ernie Rose quietly passed away in his sleep on June 2, 2015 at the age of 88.

Irwin (Ernie) Allen Rose was born July 16, 1926 in Brooklyn, New York to first-generation immigrant parents from Eastern Europe. In his early years, he enjoyed a closely knit extended family and an ethnically rich neighborhood typical of the borough. When he was 13, the family doctor advised that they move to a drier climate to counter complications from his brother's rheumatic fever. Thus, he, his mother, and siblings relocated to the "high and dry" climate of Spokane, Washington to live with his mother's sister while his father remained in Brooklyn, tending to their flooring business. During his summers, Ernie worked in the local hospital, where he developed an interest in medical research and a fascination with the workings of the brain. Ernie's initial college work at Washington State College was interrupted by naval service in the South Pacific as a radioman during the waning days of World War II. On his discharge, Ernie enrolled at The University of Chicago on the GI Bill and received his bachelor's degree in 1948, followed by his doctorate in 1952. Post-doctoral training with C.E. Carter at Western Reserve University and Severo Ochoa at New York University followed, until invited by Joseph Fruton to join the Biochemistry faculty at Yale as an Instructor. In addition to his fateful discussion with Mel Simpson during his first year at Yale, Ernie met and married Zelda Budenstein, a graduate student in the department preparing to complete her degree. Their careers and scientific interests would intertwine over subsequent decades as equal partners until Zelda's retirement in 1987 in order to devote more time to her international peace work. In 1963, Ernie and Zelda moved to the Fox Chase Cancer Center, where he remained until his retirement to Laguna Woods, California in 1995. To no one's surprise, Ernie took poorly to retirement, and his restlessness soon found him at The University of California-Irvine in good friend Ralph Bradshaw's office, looking for "a lab, a bench, anything." With a modest lab in which to resume his work and a university appointment as Distinguished Professor-in-Residence, he soon became a valuable member of the department and a mentor to graduate students, post-doctoral fellows, and faculty.



Irwin (Ernie) Allen Rose
Image courtesy of Fox Chase Cancer Center

Ernie made numerous seminal contributions during his long career in addition to those associated with ubiquitin-dependent proteolysis. He pioneered the use of isotopic methods, stereochemical studies, and various chemical and isotopic trapping methods to characterize enzyme mechanisms, especially those involving proton transfer, at levels of detail previously not possible. Many of these advancements utilized the concept of partition analysis, the careful accounting of how a substrate or an enzymatic intermediate is interconverted into various products. By measuring the exchange or transfer of a proton to solvent, product, or substrate, we learned much about the structure and underlying chemistry of catalysis long before structures of the enzymes were available. He collaborated with crystallographers, spectroscopists, and chemists to realize the full potential of these approaches. Using this tool kit, his group unambiguously demonstrated the catalytic mechanisms of enzymes involved in glycolysis and the TCA cycle, including aldolase, triose and pentose isomerases, pyruvate kinase, phosphofructokinase, hexokinase, aconitase, enolase, and carbamyl phosphate synthetase. For these and other achievements, he was elected to the National Academy of Sciences in 1978.

Yet, it remained an enduring irony to Ernie that the work for which he would become most noted was more of a side project. While he dabbled periodically in protein degradation for several decades after learning of Simpson's work, he never quite got a foothold in the field until his fateful meeting with Avram Hershko at an NIH-sponsored Fogerty Conference on Regulation in 1975. Their collaboration was a perfect match of temperaments and perspectives that did much to drive early advances in the short period spanning the late 1970s and early 1980s, ultimately leading to the discovery of ubiquitin-dependent proteolysis. It is hard to overstate how much

fun those years were. Each day brought new and puzzling observations that Ernie would absorb and reflect; each summer brought a host of visitors from Israel with fresh data and endless questions. This was "team science" long before it became a model for scientific progress.

Ernie was a modest man, always ready to credit others where due. In fact, he refused to leave his name on our *Journal of Biological Chemistry* paper describing the involvement of ubiquitin because it wasn't his "idea." He believed in being passionate about life and was passionate about discovering how things worked. He was impatient with anything or anyone who got in the way of his passion. He loved to sit and "talk science." For anyone who knew him, a recurring memory is of Ernie sitting in his cluttered office, propped back precariously in his chair discussing your newest data or some recent paper. For those astute enough to notice during these discussions, Ernie approached science with an old world sense of craftsmanship. He reveled in designing experiments that were simple and concise, if sometimes physically impossible. However, his record of insight suggested that you should find a way to do the experiment and, not surprisingly, the results would unambiguously prove the hypothesis at hand—the antithesis of contemporary "big science." These insights remain an enduring gift to those fortunate to have interacted with Ernie.

Ernie Rose is survived by Zelda, his wife of 61 years, and his sons Frederic, Robert, and Howard, a brother, and five grandchildren. He is mourned by all whose lives his indomitable curiosity and towering intellect influenced.

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http://dx.doi.org/10.1016/j.cell.2015.06.066